PhRMA

May 26, 1999

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 99D-0484 (64 Fed. Reg. 14735, March 26, 1999); Comments on FDA's "*Draft Guidance for Industry – Accelerated Approval Products – Submission of Promotional Materials*"

Dear Sir or Madam:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to provide comments on the above-referenced draft guidance for industry. PhRMA member companies are devoted to inventing medicines that enable patients to live longer, happier, healthier, and more productive lives; our members invest over $24 billion a year in discovering and developing new treatments. For this reason, PhRMA and its members are keenly interested in all aspects of the regulatory process, including the information in 21 C.F.R. 314.550 which presents the current regulations governing promotional materials for drugs subject to the provisions of the accelerated approval regulation. We also recognize and appreciate FDA's effort to prepare a draft guidance intended to assist sponsors of drugs and biologic products who are submitting promotional materials pursuant to the accelerated approval regulations. The purpose of this letter is to provide comments on this new draft guidance.

On March 26, 1999, FDA announced the availability of a new draft guidance for industry on submission of promotional materials for products subject to the accelerated approval regulations. FDA requested written comments on this draft guidance by May 26, 1999. In the paragraphs below, PhRMA provides comments on each section of the draft guidance.

Sections I (Introduction) and II (Background)
FDA published the final rule on accelerated approval on December 11, 1992 (57 *Fed. Reg.* 58942). This final rule became effective on January 11, 1993 and it has been used to grant accelerated approval to approximately 25 products to date. Therefore, PhRMA supports FDA's effort to provide standardized guidance on submission of promotional materials for products subject to the accelerated approval regulations.

PhRMA encourages FDA to add the following statement to Section II in order to clarify one aspect of the scope of this draft guidance:

> *In some cases, a drug or biologic product may have multiple indications for its use where one indication may be subject to accelerated approval, while a different indication has received traditional approval from FDA. For such a product, only those promotional materials including indications with accelerated approval are subject to the provisions of 21 C.F.R. 314.550.*

Section III (Communicating with FDA During the Preapproval Review Period)
PhRMA supports the statement in this guidance that "FDA encourages sponsors to begin communication with the appropriate division early in the application review process . . . ." FDA points out that such early communication will enable the sponsor to understand and comply with the submission requirements. However, the draft guidance does not provide specific information on the timing of such early communication; the timing of such interactions is particularly critical for products with priority (P) review status. PhRMA encourages FDA to consider adding the following new paragraphs to Section III:

> *The sponsor should talk with the reviewing division and DDMAC (or APLS) to enable submission of promotional materials (intended for dissemination within the first 120 days following accelerated approval) approximately 4 to 8 weeks in advance of the target approval date. Close interaction and communication between DDMAC (or APLS) and the sponsor are especially important for those products with a shorter review clock due to priority (P) review status.*
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> *Unless otherwise requested during the preapproval review period, the sponsor should submit all proposed promotional materials in duplicate to DDMAC or APLS, with an additional two copies provided to the division responsible for review of the regulatory application.*

Section IV-A (General Requirements for Submission and Review)
The draft guidance states that "[t]he Agency expects that materials will *not* be disseminated or published until the Agency's objections are resolved. The FDA recommends that the applicant plan sufficient time for resolving differences with the Agency concerning the submitted materials prior to dissemination or publication." Similarly, Section V of the draft guidance states that the "materials should not be used until the Agency's concerns have been resolved . . . ." These requirements go beyond the provisions of 21 C.F.R. 314.550, and, therefore, are improper.

The regulation states that the "applicant must submit to the agency for consideration during the preapproval review period copies of all promotional material intended for dissemination or publication within the 120 days following approval." It is clear that the regulation only requires a submission of materials, and not agency approval or clearance of materials. Thus, the guidance should state that the applicant is not required to wait for comments or resolution of the Agency's concerns. It is understood that the Agency has the authority to enforce all regulations and legal requirements regarding promotional advertising and labeling. Additional requirements are not warranted. As a practical matter, sponsors will generally wait for the Agency's comments and deal in good faith to resolve the issues prior to dissemination and publication. This section has particular relevance to simple reminder/coming soon-type advertisements. A sponsor should not be required to wait three weeks for comments after the submission of ads of this nature.

This section of the draft guidance should also specify a definition for "derivative" promotional materials, and provide that derivative materials are those promotional materials that are derived from prior materials but because of additional words, layout, graphics, or other representations, have new or different attributes from the prior piece.

PhRMA appreciates FDA setting the aggressive goal to usually provide comments within 15 working days of receipt of promotional materials by DDMAC or APLS. Nonetheless, PhRMA encourages you to incorporate the following sentence into the draft guidance so that applicants will allow sufficient time for review and resolution of comments:

> *Applicants should strive to submit proposed promotional materials several weeks before intended utilization in the event that additional consultation with FDA is needed.*

Section IV-B (Submissions During the 120-Day Post Approval Period)
The draft guidance recognizes that some circumstances arise where a sponsor must submit proposed promotional materials during the 120-day post-approval period for subsequent dissemination within the first 120 days post approval. For example, the guidance provides that FDA will review additional materials if there is an unforeseen problem with product administration or availability, or an unexpectedly high incidence of adverse events. The same allowance should be made for efficacy information. The promotional materials submitted prior to approval may be submitted too early to contain important efficacy data that will eventually appear in the final labeling. In such instances, the sponsor should be provided a means to include that information in the promotional materials during the 120-day postapproval period.

PhRMA understands FDA's desire to use this approach only on "rare occasions." However, the need for this approach is increasingly common due to the inability of the sponsor to receive final draft labeling from the reviewing division sufficiently in advance of accelerated approval. Without such final draft labeling, the sponsor is unable to prepare proposed promotional materials in time to enable submission and completion of review during the preapproval period. This situation may arise for a number of reasons, many of which are beyond the sponsor's control. Therefore, PhRMA suggests incorporation of the following statement in this section:

> *The sponsor may submit proposed promotional materials during the 120-day post-approval period for subsequent dissemination within the first 120 days post approval for a product where final draft labeling (which is known to be acceptable to the reviewing division) was not available to the sponsor at least 6 weeks in advance of the date of accelerated approval. Such final draft labeling is essential to serve as the basis for preparation of promotional materials.*

Also, the draft guidance states that "sponsors can request that FDA review such additional materials [*e.g.*, related to unforeseen problems] and should provide a rationale for distribution of these materials prior to submission of the actual materials." It is unclear what FDA means by this, as FDA seems to be indicating in this sentence that a sponsor might be able to distribute promotional materials prior to submission to FDA. This indication seems inconsistent with other statements in the draft guidance, and should be clarified.

Section V (Promotional Materials Intended for Use Following the 120-Day Postapproval Period)

As noted above, in PhRMA's view, Section V exceeds the regulatory requirement for submission of promotional materials on products subject to the accelerated approval regulation. For promotional materials submitted after marketing approval, 21 C.F.R. 314.550 is clear that the applicant must submit all promotional materials at least 30 days prior to initial dissemination. However, the regulation does not state that sponsors must await FDA approval prior to initiation of dissemination.

This interpretation of the regulation is entirely consistent with the preamble of the final rule (page 58950), where FDA stated its intent to review all such materials promptly and to notify the applicant of any identified problems as soon as possible. Further, FDA went on to say that the agency expects that, if the agency notifies the applicant of significant objections to the proposed materials, no materials will be disseminated or published until the agency's objections are resolved. Consistent with this interpretation, after marketing approval, the applicant would be able to submit final promotional materials to FDA at least 30 days prior to initial dissemination and then (absent significant objections from FDA during the 30 day period) initiate dissemination of the materials after at least 31 days have elapsed.

This section of the draft guidance should also clarify the requirements for "derivative materials." After the 120-day postapproval period, the Agency is requiring that all derivative materials be submitted for review prior to use. The Agency should more clearly define "derivative material" as those promotional materials that are similar to previously reviewed materials but because of additional words, layout, graphics, or other representations, a new attribute is derived. Identical, previously reviewed claims in a different format with no new product attributes should not be required to be submitted for review prior to use. Such a requirement creates an unnecessary burden for both the sponsor and the Agency. The Agency would be required to waste valuable resources on the review and comment of a submission that has already been resolved.

Finally, PhRMA recommends including a statement in the draft guidance to remind sponsors that submission of promotional materials in advance of initial dissemination does not satisfy the sponsor's separate obligation to submit the final promotional materials at the time of initial dissemination or publication with a Form FDA 2253 (see 21 C.F.R. 314.81(b)(3)(i) [requiring submission of promotional materials at the time of initial dissemination]).

Section VI (Terminating Submission Requirements)

FDA has the authority under 21 C.F.R. 314.560 to determine that, for a specific product, the regulatory requirements for pre-dissemination submission of promotional materials are no longer necessary. Congress has indicated that such advance submission of promotional materials should only be required when appropriate and "for a period of time necessary for the sponsor to demonstrate that it understands and will comply with the FDA's promotional material requirements." H.R. Rep. No. 105-310, at 56 (1997). In accordance with Congress' clear intent, when a sponsor has demonstrated a record of compliance with applicable promotional requirements, advance submission of promotional materials following accelerated approval becomes unnecessary and can be appropriately discontinued.

As a general rule, when FDA requires the advance submission of promotional materials, PhRMA suggests that the requirement should end six months following accelerated approval, or sooner if Phase IV studies that will serve as the basis of a Supplemental NDA for traditional approval are completed sooner. Once Phase IV studies are finished and reported to FDA, no basis exists to distinguish an accelerated approval product from a product approved under traditional criteria, and FDA's ordinary rules on the submission of promotional materials should apply. See 21 C.F.R. 314.81(b)(3)(i) (requiring submission of promotional materials at the time of initial dissemination). Even when Phase IV studies are not yet completed, six months provides a sufficient time for a sponsor to demonstrate its understanding of and compliance with pertinent rules and constraints for its promotional materials.

In most cases, requiring advance submission of promotional materials for a longer period of time is not justified and would not constitute a sensible use of either FDA's or the sponsor's resources. Of course, FDA must retain the authority to require the continued advance submission of promotional materials for a sponsor who has not demonstrated a record of compliance. However, for a sponsor who has demonstrated compliance, little would be gained by FDA's continued advance review of the same or similar materials year after year. FDA, of course, retains its general authority to take enforcement action against false or misleading promotion, and that authority provides appropriate safeguards (up to and including withdrawal of accelerated approval) against violative promotion without the administrative burdens of continued advance submission.

Finally, in particular cases where reason exists to maintain the requirement for advance submission even beyond six months after accelerated approval, then PhRMA requests that FDA add the following paragraph to this section of the draft guidance in order to explicitly state that the submission requirement under 21 C.F.R. 314.550 is terminated upon the approval of a Supplemental NDA for the indication or product previously subject to accelerated approval.

> *The regulatory obligation to submit all promotional materials at least 30 days prior to the intended time of initial dissemination or publication is automatically terminated as of the date of approval of a Supplemental NDA for an indication or product that was previously subject to accelerated approval.*
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We hope that these comments are useful. The PhRMA Work Group that prepared these comments is available at your convenience to answer any questions or discuss any aspects of this important draft guidance. Thank you for your consideration.

Sincerely,

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cc: Tracy L. Acker (CDER) and Toni M. Stifano (CBER)